Red Blood Cell Isoimmunisation in Pregnancy

Red blood cell isoimmunisation is the production of antibodies in response to an isoantigen that is present on an erythrocyte (Red blood cell).

Maternal isoimmunisation occurs when the mother's immune system is sensitized to antigens on fetal erythrocytes. This results in the production of immunoglobulin G antibodies. In subsequent pregnancies, these antibodies can cross the placenta and attack the fetal red blood cells leading to hemolysis and anemia in the fetus that is known as hemolytic disease of the newborn.

Causes of Rh-D isoimmunization

The placenta usually acts as a barrier between fetal blood and maternal circulation. However, during pregnancy or at birth, fetomaternal hemorrhage (FMH) can occur, when small amounts of fetal Rh-positive blood crosses the placenta and enter the Rh-negative mother's blood. The mother's immune system produces anti-D antibodies.

In subsequent pregnancies, these maternal antibodies can cross the placental barrier and destroy the red cells of any Rh-positive fetus.

Rh-D isoimmunization can result from any procedure or incident where positive blood leaks across the placenta, or from any other transfusion of Rh-positive blood. Hemolytic disease of the fetus and newborn caused by Rh-D isoimmunization can occur during the first pregnancy.

However, in most cases, sensitization during the first pregnancy or birth leads to extensive destruction of fetal red blood cells during subsequent pregnancies rather than the first pregnancy.

Pathophysiology Rh-D isoimmunization

In red blood cell isoimmunisation, maternal antibodies are formed in response to surface antigens on fetal erythrocytes. It occurs when the fetal cells enter the maternal circulation via a 'sensitizing event' – such as an antepartum hemorrhage or abdominal trauma. It can also occur during delivery.

There are rarely any problems during the primary exposure. However, in subsequent pregnancies, maternal antibodies can cross the placenta and attack the fetal red blood cells if they carry the same surface antigen. This leads to hemolysis and subsequent fetal anemia.

The most common set of antibodies responsible for this incompatibility is the Rhesus D blood group – for which individuals are either positive (RhD+) or negative (RhD-).

Rhesus D isoimmunisation is only possible in RhD- women, and occurs when they come into contact with the blood of a RhD+ fetus:

A woman is RhD-, and her partner is RhD+. She becomes pregnant with a fetus that is also RhD+. During childbirth, she comes into contact with the fetal (RhD+) blood, and antibodies are produced (known as anti-D antibodies). She later becomes pregnant with a second child that is also RhD+.

The woman's anti-D antibodies cross the placenta during this pregnancy and enter the fetal circulation, which contains RhD+ blood. They bind to the fetus' RhD antigens on its erythrocyte surface membranes.

This causes the fetal immune system to attack and destroy its own RBCs, leading to fetal anemia. This is known as hemolytic disease of the newborn (HDN).

Diagnosis and Management

There are two main blood tests considered following a sensitizing event:

Maternal blood group and antibody screen. This determines ABO and RhD blood groups and detects any antibodies directed against RBC surface antigens (except A and B).

Feto-maternal hemorrhage (FMH) test. This is also known as the **Kleihauer test**. This test assesses how much fetal blood has entered the maternal circulation. If there has been a sensitizing event after 20 weeks gestation, this test is used to determine how much anti-D immunoglobulin should be administered.

After delivery, the Rhesus status of the baby should be checked. If the baby is RhD+ (and the mother is RhD-), an FMH test should be performed, and at least 500 IU of anti-D immunoglobulin administered. The dose can be increased depending on the size of the FMH.

Less than 12 weeks' gestation

The tests are indicated in:

~ Ectopic pregnancy,

~molar pregnancy,

~termination or heavy uterine bleeding

Management

Anti-D Immunoglobulin

If a sensitizing event occurs, maternal isoimmunisation can be prevented via the administration of Anti-D immunoglobulin. It binds to any RhD+ cells in the maternal circulation, and no immune response is stimulated.

Note: Anti-D immunoglobulin is never required in RhD+ women, as they cannot generate anti-D antibodies.

Indications for Use

In Rhesus D negative women, the administration of anti-D immunoglobulin should be considered following any sensitizing event:

Invasive obstetric testing (e.g amniocentesis or chorionic villus sampling)
Antepartum hemorrhage (APH)
Ectopic pregnancy
External cephalic version
Fall or abdominal trauma
Intrauterine death
Miscarriage
Termination of pregnancy
Delivery (normal, instrument, or cesarean section)

Prevention of Rh-D isoimmunization

Most cases of Rh-D isoimmunization can be prevented by injecting anti-D Ig within 72 hours of birth or any other sensitizing event. Anti-D Ig is a human plasma-based product that is used to prevent women from producing anti-D antibodies.

Anti-D immunoglobulin is of value to women with non-sensitized Rh-negative blood who have a baby with an Rh-positive blood type.

It is not used when anti-D antibodies are already present in maternal blood. As well, anti-D immunoglobulin does not protect against the development of other antibodies that cause hemolytic disease of the newborn.

Routine prophylaxis

Institutions have adopted the routine antenatal anti-D prophylaxis at 28 and 34 weeks gestation for all non-sensitized Rh-negative women.

Antenatal prophylaxis should always be given following possible sensitization events such as spontaneous miscarriage before 12 weeks, any threatened, complete, incomplete, or missed abortion after 12 weeks of pregnancy, termination of pregnancy by surgical or medical methods regardless of gestational age, fetal death in utero or stillbirth, ectopic pregnancy or amniocentesis, cordocentesis, chorionic villus sampling, fetal blood sampling, or other invasive intrauterine procedures such as shunt insertion.

In addition, postnatal prophylaxis should be given.

Management of Rh-D isoimmunization

Destruction of fetal RBCs results in fetal anemia and less oxygen reaching fetal tissue, and edema and congestive
cardiac failure can develop. Lesser degrees of red cell destruction may result in fetal anemia only, while extensive hemolysis can cause hydrops fetalis and fetal death.

Mortality rates are higher for those with hydrops fetalis.

Early referral to specialist care for women with Rh-D antibodies detected at booking is essential. While early specialist care in?uences fetal outcome ongoing midwifery information and support are also important. Treatment aims to reduce the effects of hemolysis.

Intensive fetal monitoring is usually required, and often a high level of intervention throughout the pregnancy.

Postnatal treatment of isoimmunization

Management aims to monitor the SBR level so that early intervention can be made if the level is high or increasing
rapidly to try to prevent levels from reaching those that might be harmful. The following factors are worthy of
consideration:

• Using phototherapy from birth helps to prevent a rapid rise in some babies.
• Regular SBR measurements from birth every 4 hours.
• A low hemoglobin concentration at birth may indicate the need for early intervention with an exchange transfusion.
• If the SBR level is increasing too rapidly or is too high then intervention is required.

Treatment depends upon the baby's condition. Careful monitoring but less aggressive management may be adequate, with mild to moderate hemolytic anemia and hyperbilirubinemia. Severely affected babies often require early admission to the NICU. Babies with hydrops fetalis are pale, have edema and ascites.

In some cases, phototherapy alone can be effective and is very useful to help to prevent the need for exchange transfusion, which carries many more risks.

Despite this, exchange transfusion is often required, and later packed cell transfusion may be needed to increase hemoglobin levels as babies are at risk of ongoing hemolytic anemia and this may occur up to 6–8 weeks of age.

Treatment with IVIG can be effective at blocking ongoing hemolysis, with a shorter duration of phototherapy and fewer exchange transfusions although this may also increase the likelihood of a later 'top-up' blood transfusion